Remarks

I. Support for the Amendments

The amendment to the specification is sought to update the cross-reference section (specifically to enter the U.S. Patent number for the parent application), and therefore adds no new matter.

The amendment to claim 7 deletes subject matter from this claim, and therefore adds no new matter.

Support for the remaining amendments to the claims may be found in the original claims as filed and throughout the specification, inherently or explicitly. Specifically, support for the amendments to claims 1, 2, 23 and 66 may be found at page 12, lines 16-28 and page 30, line 27 to page 31, line 1. Support for the amendments to claim 21 may be found at page 9, lines 3-14. Hence, these amendments do not add new matter, and their entry and consideration are respectfully requested.

Support for new claims 69-72 may be found in the original claims as filed and throughout the specification, inherently or explicitly. Specifically, support for new claims 69-72 may be found at page 24, line 29 to page 25, line 18. None of the art cited in Paper No. 7 discloses or suggests these new claims. These amendments do not add new matter, and their entry and consideration are respectfully requested.

II. Status of the Claims

By the foregoing amendments, claim 3-4, 34-37, 39-42, 52-65 and 67-68 have been cancelled without prejudice or disclaimer, and claims 1-2, 7, 21, 23 and 66 have been amended. These amendments do not introduce new matter into the application. Upon entry of the foregoing amendments, claims 1-2, 5-33, 66 and 69-72 are pending in the application, with claims 1, 2, 23 and 66 being the independent claims.

III. Summary of the Office Action

In the Office Action dated June 19, 2002, the Examiner has made one objection to and four rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each of these elements of the Office Action.

IV. Information Disclosure Statement

Applicants first note that, at page 2 of the Office Action, the Examiner has indicated that Document Nos. AH1, AI1, AB2, AE2, AF2, AI3, AN3, AR11, AS11, AT11, and AR12, cited in Applicants's Information Disclosure Statement ("IDS") filed on October 5, 2001, have not been considered by the Examiner because copies of these documents were allegedly not supplied either in the present application or the parent application. Applicants respectfully disagree, and note that copies of these documents were included with the IDS, as evidenced by the return receipt postcard bearing the PTO date stamp of that date (copy enclosed). Applicants enclose herewith copies of these documents for the convenience of the Examiner, and respectfully request that the Examiner consider these documents and

indicate their consideration on the record. Notice of consideration of these documents is respectfully requested in the next communication from the Examiner.

V. Rejection under 35 U.S.C. § 112, Second Paragraph

In the Office Action at pages 2-3, the Examiner has rejected claims 7-8, 21-22 and 66 under 35 U.S.C. § 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants respectfully traverse this rejection.

The Examiner has rejected claims 7-8 as allegedly being indefinite for recitation of the language "derivatives thereof." *See* Office Action at page 3. Solely to advance prosecution and not in acquiescence to the rejection, Applicants have deleted the language "derivatives thereof" from claim 7. Accordingly, Applicants respectfully request reconsideration and withdrawal of this portion of the rejection.

The Examiner has next rejected claim 66 as allegedly being indefinite because of its dependency from non-elected claim 34. By the foregoing amendments, claim 66 has been amended to delete its dependency from non-canceled claim 34, as suggested by the Examiner. Accordingly, Applicants respectfully request reconsideration and withdrawal of this portion of the rejection.

The Examiner has also rejected claims 21-22 as allegedly being indefinite because it is unclear whether or not the first individual is also prepared according to the method of claim 1. *Id.* Solely to advance prosecution and not in acquiescence to the rejection, Applicants have amended claim 21 (and thus the dependent claim 22) to recite "wherein said DNA samples of said first and second individuals are analyzed according to the method of

claim 1." Accordingly, Applicants respectfully request reconsideration and withdrawal of this portion of the rejection.

In view of the foregoing remarks, Applicants respectfully asserts that claims 7-8, 21-22 and 66 particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

VI. Rejection Under 35 U.S.C. § 102(b) Over the '188 Patent

In the Office Action at pages 3-4, the Examiner has rejected claims 1-2, 5 and 66 under 35 U.S.C. § 102(b) as allegedly being anticipated by Mullis *et al.*, U.S. Patent No. 4,965,188 (Doc. B on the Form PTO-892 attached to Paper No. 7; hereinafter "the '188 patent"). Applicants respectfully traverse this rejection.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single enabling prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). This requirement is not met by the disclosure of the '188 patent, which therefore cannot anticipate the invention as presently claimed.

The Examiner asserts that:

> Mullis et al. disclose a method of amplifying any target nucleic acid sequence (See the abstract). The target nucleic acid sequence is a polymorphic DNA fragment (See column 22, lines 24-28). The polymerase is Klenow fragment (See

> column 35, lines 5-15) which has ability to reduce to add [sic] one or more non-templated nucleotide to the 3' terminus of a DNA molecule. Therefore, the teachings of Mullis et al. anticipate the limitations of claims 1-2 and 5.

Office Action at page 4, lines 1-5. Applicants respectfully disagree with these assertions. Claim 1 (and claim 5 dependent therefrom) is drawn to a method of identifying, analyzing or typing a polymorphic DNA fragment in a sample of DNA comprising DNA polymerases that are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule. Claim 2 is drawn to a method of producing amplified copies of a polymorphic DNA fragment which comprise substantially no non-templated 3' terminal nucleotides by contacting a DNA sample with one or more DNA polymerases that are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule. It is well known to one of ordinary skill in the art that the Klenow fragment is the large fragment of the *E. coli* DNA polymerase I, without the 5'-3' exonuclease domain. *See* specification at page 63, lines 12-21. Thus, the Klenow fragment disclosed in the '188 patent is not a DNA polymerase that has been mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule. Furthermore, there is no disclosure in the '188 patent of any polymerase that is substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule. Therefore, this reference cannot and does not anticipate the claimed invention.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) over the '188 patent be reconsidered and withdrawn.

VII. Rejections Under 35 U.S.C. §§ 102(e)/103(a) Over the '668 Patent

In the Office Action at pages 4-5, the Examiner has rejected claims 1-2, 5-19 and 23-33 under 35 U.S.C. § 102(e) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as unpatentable over, Hughes *et al.*, U.S. Patent No. 6,015,668 (Doc. AG3, of record; hereinafter "'668 patent"). Applicants respectfully traverse this rejection.

A. The Rejection Under 35 U.S.C. § 103(a)

As a first matter, Applicants respectfully traverse this rejection as it may be applied under 35 U.S.C. § 103(a). Effective November 29, 1999, "[s]ubject matter developed by another person, which qualifies as prior art only under subsection (e), (f), and or (g) of section 102 of this title, shall not preclude patentability under [35 U.S.C. § 103] where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." 35 U.S.C. § 103(c). This statutory provision "applies to all utility, design and plant patent applications filed on or after November 29, 1999, including continuing applications filed under 37 C.F.R. 1.53(b), continued prosecution applications filed under 37 C.F.R. § 1.53(d), and reissues." MPEP § 706.02(l)(1) (February 2000). Applicants note that the '668 patent and the present invention were, at the time the present invention was made, owned by or subject to an obligation of assignment to a common assignee: Life Technologies, Inc., (which has since merged with, and therefore is predecessor in interest to, Invitrogen Corporation). Applicants respectfully assert that the '668 patent, qualifies (if at all) as prior art only under § 102(e), as acknowledged by the Examiner in the present Office Action. Hence, under 35 U.S.C. § 103(c), the disclosure of the '668 patent is not available as prior

art against the present application under 35 U.S.C. § 103(a). This portion of the rejection therefore is in error and must be withdrawn.

B. The Rejection Under 35 U.S.C. § 102(e)

Alternatively, Applicants also traverse the rejection of claims 1-2, 5-19 and 23-33 under 35 U.S.C. § 102(e) over the '668 patent. The '668 patent does not disclose every element of these claims, expressly or inherently, for the following reasons.

(i) The '668 Patent Does Not Expressly Disclose The Claimed Invention

Claims 1 and 2 (and thus the remaining claims that depend therefrom) are drawn to methods comprising DNA polymerases that are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule. Claim 23 (and thus the remaining claims that depend therefrom) is drawn to a kit comprising DNA polymerases that are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule. There is no express disclosure in the '668 patent of any DNA polymerase that is mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule. On the contrary and as the Examiner acknowledges (*see* Office Action at page 4, lines 13-14), the '668 patent does not expressly indicate that the polymerase is substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule as claimed. Thus, the '668 patent fails to expressly anticipate the claimed invention.

(ii) The '668 Patent Does Not Inherently Disclose The Claimed Invention

Perhaps recognizing these deficiencies in the disclosure of the '668 patent, the Examiner instead appears to contend that this document *inherently* discloses the present invention. For example, the Examiner contends that:

> the DNA polymerase of Hughes et al. is inherent that the DNA polymerase has the ability to substantially reduce to add [sic] one or more non-templated nucleotides to the 3' terminus of a DNA molecule as claimed and Hughes et al. also indicate that the DNA polymerase may be used in well-known amplification reaction.

Office Action at pages 4-5. Applicants respectfully disagree with these contentions. The Examiner is reminded that "[i]n order for a disclosure to be inherent . . . the missing descriptive matter must necessarily be present in the [cited reference] such that one skilled in the art would recognize such a disclosure." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998). Moreover, to rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). That is, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). In the present case, the Examiner has pointed to no disclosure in the '668 patent that is "necessarily present" such that it would be recognized as by one of ordinary skill as disclosing polymerases that are mutated to be substantially reduced in the ability to add non-templated 3' nucleotides to a nucleic acid molecule (thus, the *Tronzo* standard is not met by

the '668 patent). Merely because a polymerase is mutated in one or more positions of its O-helix tells nothing of the ability or inability of this enzyme to add non-templated 3' nucleotides to a nucleic acid molecule. Thus, the Examiner has pointed to no disclosure in the '668 patent, and has provided no sound scientific reasoning, to support the notion that the missing disclosure in the '668 patent "*necessarily* flows" from what *is* disclosed in this document (thus, the *Levy* standard is not met by the '668 patent). Moreover, one of ordinary skill reading the '668 patent could find no disclosure indicating that it was even possible, let alone probable, that polymerases could be obtained that were substantially reduced in the ability to add non-templated 3' nucleotides to a nucleic acid molecule (thus, the *Continental Can* standard is not met by the '668 patent). Thus, basing a rejection of claims 1, 2 and 23 (and the remaining claims depending therefrom) on inherent anticipation is legal error.

Furthermore, simply because a polymerase may be "used in well-known amplification reaction[s]" says *nothing* about the ability or inability of that polymerase to add non-templated 3' nucleotides to a product nucleic acid molecule. For example, wild-type *Taq* is also "used in well-known amplification reaction[s]" (as one of ordinary skill would be well-aware), since this polymerase is routinely used for DNA amplification methodologies such as PCR. However, wild-type *Taq* consistently adds non-templated 3' nucleotides to the product molecules synthesized by this enzyme, as is clearly discussed in the present specification at page 6, lines 15-23. Hence, wild-type *Taq*, which is "used in well-known amplification reaction[s]," nonetheless is *not* reduced in the ability to add non-templated 3' nucleotides to a product molecule. Therefore, the "usefulness" of a polymerase in DNA amplification is absolutely irrelevant to the ability of that enzyme to not add non-templated 3' nucleotides to a product molecule, and hence cannot form the basis for an

inherent anticipation rejection of the presently claimed invention. Hence, the Examiner's attempted reliance upon inherent anticipation in the present case is factually, legally and logically unfounded.

C. Summary

In view of the foregoing remarks, Applicants respectfully assert that the '668 patent does not expressly or inherently disclose all of the elements of the invention as presently claimed. Moreover, the '668 patent is not available as prior art against the presently claimed invention under 35 U.S.C. § 103(a). Hence, claims 1-2, 5-19 and 23-33 are neither anticipated under 35 U.S.C. § 102(e), nor rendered obvious under 35 U.S.C. § 103(a), by the '668 patent. Reconsideration and withdrawal of this rejection therefore are respectfully requested.

VIII. Rejection under 35 U.S.C. § 103(a) Over the '668 Patent In View of the '535 Patent

In the Office Action at pages 5-6, the Examiner has rejected claims 1-2, 5-19 and 23-33 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '668 patent in view of Huo, U.S. Patent No. 5,922,535 (Doc. A on the Form PTO-892 attached to Paper No. 7; hereinafter "the '535 patent"). Applicants respectfully traverse this rejection.

As noted above under 35 U.S.C. § 103(c), the '668 patent cannot form the basis of an obviousness rejection of the claims of the present application. Therefore, the primary reference upon which this rejection is based is not available as prior art. The '535 patent also does not disclose, suggest or otherwise contemplate the present invention. Therefore, a

prima facie case of obviousness has not been established. Reconsideration and withdrawal of this rejection therefore are respectfully requested.

IX. Other Matters

A. The Objection to Claim 20

Applicants acknowledge that the Examiner has objected to claim 20 in the Office Action at page 6, section 11, and has stated that claim 20 would be allowable if rewritten in independent form. In view of the foregoing remarks, Applicants respectfully assert that claim 1 is allowable and, consequently, that claim 20 in dependent form is also allowable. Reconsideration and withdrawal of this objection are therefore respectfully requested.

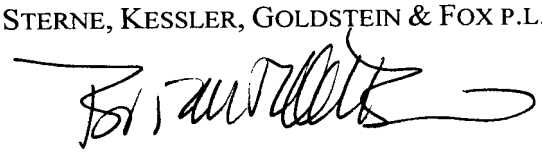
X. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Version with markings to show changes made

In the Specification:

Please substitute the first full paragraph on page 1 (the Cross Reference section appearing at lines 4-9) with the following paragraph:

This application is a divisional of U.S. Application No. 09/019,160, filed February 6, 1998 (now U.S. Patent No. 6,306,588), which claims priority to U.S. Provisional Application No. 60/037,393, filed February 7, 1997, and to U.S. Provisional Application No. 60/070,562, filed January 6, 1998, the disclosures of which are fully incorporated herein by reference.

In the Claims:

(a) Claims 3-4, 34-37, 39-42, 52-65 and 67-68 are canceled.

(b) Claims 69-72 are sought to be added.

(c) Claims 1-2, 7, 21, 23 and 66 are amended as follows:

1. (Once Amended) A method of identifying, analyzing or typing a polymorphic DNA fragment in a sample of DNA, said method comprising contacting said sample of DNA with one or more DNA polymerases, wherein said DNA polymerases are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule[,]; amplifying said polymorphic DNA fragment within said sample; and analyzing said amplified polymorphic DNA fragment.

2. (Once Amended) A method of producing amplified copies of a polymorphic DNA fragment which comprise substantially no non-templated 3' terminal nucleotides, said method comprising contacting a DNA sample with one or more DNA polymerases, wherein said DNA polymerases are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule; and amplifying said polymorphic DNA fragment within said DNA sample.

7. (Once Amended) The method of claim 6, wherein said thermostable DNA polymerases are *Thermotoga* DNA polymerases [and] or mutants [or derivatives] thereof.

21. (Once Amended) A method of determining the relationship between a first individual and a second individual, said method comprising comparing a population of amplified DNA molecules in a sample of DNA from said first individual to that of said second individual, wherein said DNA samples of said first and second individuals are [prepared] analyzed according to the method of claim 1.

23. (Once Amended) A kit [for the identification, analysis or typing of a polymorphic DNA fragment, said kit] comprising one or more DNA polymerases, wherein said DNA polymerases are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule.

66. (Once Amended) A method for amplifying a double stranded DNA molecule, comprising:

(a) providing a first and second primer, wherein said first primer is complementary to a sequence at or near the 3'-termini of the first strand of said DNA molecule and said second primer is complementary to a sequence at or near the 3'-termini of the second strand of said DNA molecule;

(b) hybridizing said first primer to said first strand and said second primer to said second strand in the presence of the one or more DNA polymerases which have been mutated to reduce, substantially reduce or eliminate the ability of the polymerases to add non-templated 3' nucleotides to a synthesized nucleic acid molecule under conditions such that a third DNA molecule complementary to said first strand and a fourth DNA molecule complementary to said second strand are synthesized;

(c) denaturing said first and third strand, and said second and fourth strands; and

(d) repeating steps (a) to (c) one or more times.